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EP-A-0 056 721
EP-A-0 181 491
NUCLEIC ACIDS RESEARCH, vol. 10, no. 20, October 25, 1982, Oxford - ARLINGTON M.J. GAIT et al. "Rapid synthesis of oligodeoxyribonucleotides VII. Solid phase synthesis of oligodeoxyribonucleotides by a continuous flow phosphotriester method on a kieselguhr-polyamide support" pages 6243-6254

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Description

This invention relates to an apparatus for the chemical synthesis of oligonucleotides.

It is known from Letsinger et al, Nucleic Acids Research 1975, vol. 2, pages 773—786, that oligonucleotides may be chemically synthesised by the sequential addition of suitably elaborated nucleoside derivatives to a shorter oligonucleotide which is covalently linked to a solid polystyrene support. Other types of solid support have also been used for this purpose, for example, cellulose, as described by Crea and Horn, Nucleic Acids Research 1980, vol. 8, pages 2331—2348, polyacrylamide, as described by Gait et al, Nucleic Acids Research, 1982, vol. 10, pages 6243—6254, silica, as described by Caruthers et al, Tetrahedron Letters, 1980, vol. 21, pages 719—722, and controlled-pore glass, as described by Sproat et al, Tetrahedron Letters, 1983, vol. 24, pages 5771—5774. In these known methods, the simultaneous synthesis of several different oligonucleotides can be accomplished only by performing each synthesis independently, thus demanding considerable investment in equipment and operator time.

Simultaneous synthesis of several different olifonucleotides has been described by Frank et al, Nucleic Acids Research, 1983, vol. 11, pages 4365—4377, using cellulose discs as the solid support. However, this method is very laborious in that each individual disc must be dried and sorted at the conclusion of each stage of the synthesis, and thereafter transferred to the appropriate reaction vessel prior to the next stage. This complex procedure enhances the probability of failure of a synthesis caused by moisture absorption during handling, or by operator error during the sorting process. In addition, the quantity of each oligonucleotide that may be prepared in any single synthesis is limited by the capacity of the cellulose disc used. Furthermore, the method is only capable of application to synthetic methods employing solid support materials which can readily be formed into coherent, mechanically stable discs.

I have now found that the simultaneous synthesis of several different oligonucleotides may be accomplished, advantageously in a convenient and rapid manner amenable to automation, by use of a suitable apparatus.

According to the present invention, there is provided an apparatus for carrying out a multiplicity of different sequential chemical syntheses on solid supports simultaneously comprising a multiplicity of support plates each formed with passageways therethrough, one of said passageways through each support plate containing a reaction chamber having a solid support; said other passageways each providing a bypass channel without a solid support, said other passageways and reaction chamber being disposed equi-angularly and at the same radial distance about an axis of each support plate means for holding said support plates in rotatable alignment about said axis in compression and in face-to-face fluid tight relationship to permit passage of a multiplicity of different fluid streams through passageways in all the plates of the apparatus when all the plates are suitably aligned; and means for independently rotating each support plate whereby each reaction chamber of each support plate may be isolated from or positioned in any one of the fluid streams.

The invention further provides a method for carrying out a multiplicity of different chemical syntheses simultaneously which comprises providing apparatus as aforesaid and for each step adjusting the positions of the plates according to the compounds to be synthesised, applying pressure to the plates, passing reactant streams through the plates and releasing said pressure to permit the plate positions to be adjusted in the next following step.

The work "Teflon" used hereinafter is a Registered Trade Mark.

Specific embodiments of the invention will now be described, by way of example, with reference to the accompanying drawings, in which:—

Figure 1 shows in side view the assembed apparatus;

Figure 2 shows in plan view one of the end-plates of the apparatus;

Figure 3 shows in plan view one of the movable plates of the apparatus;

Figure 4 shows in cross-section the construction of the reaction chamber in the movable plates;

Figure 5 shows in plan view one of the fixed plates of the apparatus; and

Figure 6 shows diagrammatically an apparatus with automatically rotated plates.

Referring to the drawings, the apparatus comprises two end-plates 1, 2 to each of which are attached tubes 3, 4, 5, 6 and 7, 8, 9, 10 for the passage of fluids through the apparatus, two fixed plates 13, 14 which engage in locating pins 31, 32 on the end-plates 1, 2 by means of drilled holes 44, 45 so that the fluid passages 47, 48 49, 50 align with the tubes 3, 4, 5, 6 of the end-plate 1, and twelve rotating plates 15—26 inclusive fitted between the two fixed plates, the whole assembly being held together by clamp bolt 11 and nut 12 passing through the central holes 30, 33 and 46 of the individual components.

Each rotating plate 15—26 contains four fluid passages 35, 36, 37, 38 and a reaction chamber 39 equipped with a fluid outlet 40, all arranged symmetrically about the central hole 33, and is equipped with a pin 34 by means of which the plate may be rotated about the central bolt 11.

When the apparatus is in use, the reaction chamber 39 contains a solid-support material 42 held in place by porous discs 41, 43.

Preferred materials for the construction of the components of the apparatus are stainless steel for the end-plates 1, 2 and the pin 34, polytetrafluoroethylene for the plates 13, 14, 15—26 and porous discs 41, 43 and either of these materials for the tubes 3—10 inclusive.

Additional clamp bolts may be fitted between the holes 27, 28, 29 of the end plates to facilitate operation at high fluid pressures.

The number of rotating plates in the apparatus may be increased or reduced according to requirements.

In use, the apparatus is connected by means of the tubes 3, 4, 5, 6 to four fluid streams containing, in solution, suitably elaborated derivatives of the four common nucleosides, together with any necessary catalyst or activatiing agent.

At each stage of the synthesis, each rotating plate 15—26 of the apparatus is aligned so that the solid-support material 42 contained in the reaction chamber 39 contacts whichever of the four fluid streams is approprate to the synthesis of the particular oligonucleotide being prepared on the solid-support material 42 contained in that plate. Alternatively, any of the rotating plates 15—26 may be aligned in a fifth position in which the solid-support material 42 in that plate is isolated from all four fluid streams. This feature provides for the simultaneous synthesis of oligonucleotides containing different numbers of nucleoside units, by allowing further elongation of some oligonucleotide chains without affecting those which have already been completed. Alignment of each rotating plate 15—26 of the apparatus may be performed manually or by use of a mechanical positioning device. In the latter case, the apparatus may form part of a device which performs all synthetic operations automatically.

The apparatus may be applied to the synthesis of both Ribonucleic acid and Deoxyribonucleic acid molecules by use of appropriate nucleoside derivatives during the synthesis. It may be adapted to the synthesis of other types of biological molecules which can be synthesised by stepwise addition of units to a solid-support, for example oligopeptides and oligosaccharides.

A version of the apparatus with automatic angular adjustment of the individual discs is shown in Figure 6. The stack of discs 61 rotatably supported on a central stainless steel Teflon® coated spindle 70 stands on a Teflon® base 68 that locates the discs and is provided with a fluid outlet. A protective stack header 66 allows feed tubes 3—6 from an injection port 72 to deliver reactant to the four flow channels through the stack. Each disc in the stack is about 40 mm in diameter and about 6 mm thick and when under no pressure they are freely rotatable on the spindle 79. The approximate angular position of each disc is indicated by a dot code formed by coloured Teflon® inserts on the disc edge. All the discs may be working discs formed with four holes 35—38 and a reaction chamber 39 but if desired the height may be made up by dummy discs having five through holes and free from colouring coding inserts. Each disc has its edge surface slightly knurled for good grip with a friction drive wheel (described below).

A pneumatic pressure cylinder 62 presses downwardly onto the header 66 to provide the compressive force needed to seal the disc to disc interfaces once the positions of the individual discs have been properly arranged. The actual force is controlled by an air pressure regulator and the travel of the piston is determined by a magnetically operated piston position sensor array 71 or a linear port to give an accuracy ±0.1 inches (0.25 cms) which is sufficient to confirm the number of discs in the stack 61 and thereby to define the number of vertical positions through which a disc rotation mechanism has to pass to position each disc in the stack 61. The cylinder 62 is preferably of the spring return type and the miniature valves for controlling the compressed air are suitably incorporated into an interface box 73. It is understood that the cylinder 62 is operated to maintain pressure on the disc stack 61 while reactants are being passed, but that it is retracted to relieve the pressure while the position of the discs in the discs in the stack is being changed for the next following synthesis step.

A body 65 of a disc rotation mechanism is supported for vertical movement on a worm drive rod 64 which is rotated by motor 70 and gearbox 67 which includes a cogged belt driving a wheel (not shown) engaged with the rod 64. The shaft of the motor 70 carries an encoder disc 81 movement of which is monitored by sensor 69 to enable the distance through which the body 65 has moved to be ascertained. The motor 70 may be a stepping motor or a geared DC motor. The discs in the stack 61 are each formed with an extra 5 quarter inch (0.6 cm) holes in their periphery to permit a location pin 63 to pass through. The pin 63 is also worm driven from the motor 70 via the gearbox 67 and cogged belt, and the gearbox 67 ensures a direct 1:1 relationship between the vertical travel of the pin 63 and the body 65. The cogged rubber belt transmission requires no lubrication and is self-adjusting by means of a spring loaded jockey wheel. The rod 63 is at its lower end in the form of a quarter inch (0.6 cm) Teflon® coated tapered rod that is moved stepwise downwardly one disc thickness behind the body 65 so that the disc whose position has just been adjusted together with any overlying discs is immobilised during adjustment of the angular position of the next following disc. Locking is by passage of the rod 63 through the quarter inch (0.6 cm) diameter peripheral holes in the disc stack 61.

The body 65 on the rod 64 includes an air operated ram that moves a drive assembly 75 to and from engagement with a selected disc in the stack 61. An electric motor 77 and gearbox drive a drive wheel 76 that engages the edge of the selected disc to effect rotation thereof, a disc position photocell 78 counting the disc edge dot code to monitor disc position. When the correct disc position has been detected, the assembly 75 is retracted after which the motor 70 is energised to engage the pin 63 with the newly positioned disc and to index the assembly 75 into engagement with the next disc to be positioned.

The interface unit 73 provides pneumatic lines

82, 83 to the cylinder 62 and to the cylinder in body 65 and contains logic units to enable the apparatus to be initialised. Thus the cylinder 62 will be operated once to allow the number of discs in the stack 61 to be sensed. A control channel such as an RS 232 port is provided for interface with a host computer to provide for positioning instructions for the several discs. The host computer will also control the chemical supply via injection ports 72. Internal DIP switches may be provided to adjust the baud rate parity and other parameters of the RS 232 port.

Claims

1. Apparatus for carrying out a multiplicity of different sequential chemical synthesis on solid supports simultaneously comprising a multiplicity of support plates (15—26) each formed with passageways therethrough, one of said passageways through each support plate containing a reaction chamber (39) having a solid support (42); said other passageways (35—38) each providing a bypass channel without a solid support, said other passageways (35—38) and reaction chamber (39) being disposed equi-angularly and at the same radial distance about an axis (33) of each support plate (15—26), means (11, 12) for holding said support plates (15—26) in rotatable alignment about said axis (33) in compression and in face-to-face fluid tight relationship to permit passage of a multiplicity of different fluid streams through passageways in all the plates (15—26) of the apparatus when all the plates (15—26) are suitably aligned; and means (34) for independently rotating each support plate (15—26) whereby each reaction chamber (39) of each support plate (15—26) may be isolated from or positioned in any one of the fluid streams.

2. Apparatus according to Claim 1, wherein said holding means includes end plates (13, 14) complementary to the support plates (15—26) and each formed with a blank position and passages for the fluid streams.

3. Apparatus according to Claim 1 or 2, wherein there are four by-pass channels (35—38) in each support plate (15) and four reactant streams.

4. Apparatus according to Claim 1, 2 or 3, wherein the support plates (15—26) are of polytetrafluoroethylene.

5. Apparatus according to any preceding claim, wherein the reaction chamber (39) in each support plate (15—26) contains a pair of spaced porous plates (41, 43) between which the solid support (42) is held.

6. Apparatus according to any preceding claim, wherein the support plates (15—26) are formed with central through-holes (33) through which a pin passes to provide rotatable support for said plates.

7. Apparatus according to any preceding claim, wherein there are also present dummy plates formed with at least five symmetrically positioned through holes and no reaction chamber.

8. Apparatus according to any preceding claim, further comprising a plate rotation head (65, 75) operable to engage a selected plate (15—26) to effect rotation thereof, means (64, 67) for indexing the rotation head (65, 75) stepwise along the plates (15—26) and a locator pin (63) engageable in one of a set of locator holes in each plate and indexed stepwise so that when the rotation head is engaging the mth plate in a stack of n plates wherein $1<m<n$ the newly aligned plates from 1 to $(m-1)$ are engaged with the locator pin (63).

9. Apparatus according to Claim 7, wherein the locator pin (63) and plate rotation head (65) are driven by worms rotated by a common drive motor and gear box (67).

10. Apparatus according to Claim 8 or 9, wherein a double-acting ram engages the locator head with and withdraws it from engagement with each plate.

11. Apparatus according to Claims 8 to 10, wherein the edges of the plates are provided with optical markings and the plate rotation head includes a sensor that senses passage of the markings.

12. Apparatus according to Claims 8 to 11, including a ram (71) operable to apply pressure to the plates during passage of reactants and to release said pressure during indexing.

13. Apparatus according to Claim 12, wherein the ram (71) includes a position sensor operable to detect an extended position thereof from which the number of plates present can be detected.

14. A method for carrying out a multiplicity of different sequential chemical syntheses simultaneously which comprises providing apparatus as claimed in Claims 1—13, and for each step adjusting the positions of the plates according to the compounds to be synthesised, applying pressure to the plates, passing reactant streams through the plates and releasing said pressure to permit the plate positions to be adjusted in the next following step.

15. A method according to Claim 14, wherein the compounds to be synthesised are oligonucleotides.

Patentansprüche

1. Vorrichtung zur Ausführung einer Vielzahl von verschiedenen aufeinanderfolgenden chemischen Synthesen auf festen Trägern mit einer Vielzahl von Trägerplatten (15—26), von denen jede mit sich durch diese erstreckenden Leitungen versehen ist, wobei eine dieser sich durch jede Trägerplatte erstreckenden Leitungen eine Reaktionskammer (39) mit einem festen Träger (42) aufweist und die anderen Leitungen (35—38) jede einen Bypass-Kanal ohne festen Träger bilden, wobei die anderen Leitungen (35—38) und die Reaktionskammer (39) in gleichen Winkelabständen voneinander und mit gleichem radialen Abstand um eine Achse (33) jeder Trägerplatte (15—26) angeordnet sind, Mittel (11, 12) zur Halterung der Trägerplatten (15—26) in drehbarer Ausfluchtung um die Achse (33) unter Druck und in gegenüberliegender flüssigkeitsdichter Bezie-

hung vorgesehen sind, um die Passage einer Vielzahl von unterschiedlichen Fluidströmen durch die Leitungen in allen Platten (15—26) der Vorrichtung zu ermöglichen, wenn alle Platten (15—26) entsprechend ausgefluchtet sind und Mittel (34) zur voneinander unabhängigen Drehung jeder Trägerplatte (15—26) vorgesehen sind, wodurch jede Reaktionskammer (39) jeder Trägerplatte (15—26) isolierbar von oder positionierbar in einem jeden der Fluidströme ist.

2. Vorrichtung nach Anspruch 1, dadurch gekennzeichnet, daß die Haltemittel Endplatten (13, 14) aufweisen, die komplementär zu den Tragplatten (15—26) sind und von denen jede mit einer Leerposition und mit Leitungen für die Fluidströme geformt ist.

3. Vorrichtung nach Anspruch 1 oder 2, dadurch gekennzeichent, daß vier Bypass-Kanäle (35—38) in jeder Trägerplatte (15) und vier Reaktandenströme vorgesehen sind.

4. Vorrichtung nach Anspruch 1, 2 oder 3, dadurch gekennzeichnet, daß die Trägerplatten (15—26) aus Polytetrafluoroethylen bestehen.

5. Vorrichtung nach jedem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß die Reaktionskammer (39) in jeder Trägerplatte (15—26) ein Paar von mit Abstand angeordneten porösen Platten (41, 43) aufweist, zwischen denen der feste Träger (42) gehalten ist.

6. Vorrichtung nach jedem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß die Trägerplatten (15—26) mit zentrischen Bohrungen (33) versehen sind, durch die sich ein Stift zur Schaffung einer drehbaren Halterung der Platten erstreckt.

7. Vorrichtung nach jedem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß auch Blindplatten vorgesehen sind, mit wenigstens fünf symmetrisch angeordneten Bohrungen und keiner Reaktionskammer.

8. Vorrichtung nach jedem der vorhergehenden Ansprüche, gekennzeichnet durch einen Plattenrotationskopf (65, 75) der betätigbar ist, um eine ausgesuchte Platte (15—26) zwecks Drehung derselben zu ergreifen, Mittel (64, 67) zur Inderierung des Rotationskopfes (65, 75) schrittweise längs der Platten (15—26) und einen Lokalisierungsstift (63), der in eine von einer Reihe von Lokalisierungsöffnungen in jeder Platte eingreifbar ist und schrittweise indexierbar ist, so daß beim Eingriff des Rotationskopfes mit der m—ten-Platte in einem Stapel von n-Platten bei 1—m—n die neu ausgefluchteten Platten von 1 bis (m—1) mit dem Lokalisierungsstift (63) in Eingriff sind.

9. Vorrichtung nach Anspruch 8, dadurch gekennzeichnet, daß der Lokalisierungsstift (63) und der Plattenrotationskopf (65) durch Spindeln angetrieben sind, die mittels eines gemeinsamen Antriebsmotors und Getriebes (67) drehbar sind.

10. Vorrichtung nach Anspruch 8 oder 9, dadurch gekennzeichnet, daß eine doppelt wirkende Presse mit dem Lokalisierungskopf zusammenwirkt und ihn vom Eingriff mit jeder Platte zurückzieht.

11. Vorrichtung nach Anspruch 8 bis 10, dadurch gekennzeichnet, daß die Ränder der Platten mit optischen Markierungen versehen sind und der Plattenrotationskopf einen Sensor aufweist, der das Passieren der Markierungen anzeigt.

12. Vorrichtung nach Anspruch 8 bis 11, gekennzeichnet durch eine Presse (71), die während der Passage der Reaktanden Druck auf die Platten ausübt und während der Indexierung drucklos ist.

13. Vorrichtung nach Anspruch 12, dadurch gekenzneichnet, daß die Presse (71) einen Positionssensor aufweist, der betätigbar ist, um eine aufgefahrene Stellung anzuzeigen, woraus die Anzahl der vorhandenen Platten anzeigbar ist.

14. Verfahren zur Ausführung einer Vielzahl von unterschiedlichen aufeinanderfolgenden chemischen Synthesen, bei dem Vorrichtungen gemäß den Ansprüchen 1 bis 13 verwendet werden und für jeden Schritt, bei dem die Stellungen der Platten entsprechend den zu synthetisierenden Zusammensetzungen justiert werden, Druck auf die Platten aufgebracht wird, Reaktandenströme durch die Platten strömen und der Druck entspannt wird, um eine adjustierung der Plattenstellungen für den näckstfolgenden Schritt zu ermöglichen.

15. Verfahren nach Anspruch 14, dadurch gekennzeichnet, daß die zu synthetisierenden Zusammensetzungen Oligonukleotide sind.

Revendications

1. Appareil pour effectuer une multiplicité de synthèses chimique successives différentes sur des supports solides comprenant simultanément une multiplicité de plaques de support (15 à 26) traversées chacune par des passages, l'un de ces passages à travers chaque plaque de support contenant une chambre de réaction (39) munie d'un support solide (42); les autres passages (35 à 38) formant chacun un passage de dérivation sans support solide, ces autres passages (35 à 38) et la chambre de réaction (39) étant disposée dans des positions angulaires équidistantes et à la même distance radiale autour d'une axe (33) de chaque plaque de support (15 à 26); des moyens (11, 12) pour maintenir les plaques de support (15 à 26) en alignement de rotation autour de l'axe (33), dans une relation de compression et de disposition face à face étanche au fluide pour permettre le passage d'une multiplicité de courants de fluide différents dans les passages de toutes les plaques (15 à 26) de l'appareil lorsque toutes les plaques (15 à 26) sont convenablement alignées; et des moyens (34) pour faire tourner indépendamment chaque plaque de support (15 à 26) de façon que chaque chambre de réaction (39) de chaque plaque de support (15 à 26) puisse être isolée de l'un quelconque des courants de fluide, ou placée dans l'un quelconque des courants de fluide.

2. Appareil selon la revendication 1, caractérisé en ce que les moyens de maintien des plaques de support comprennent des plaques d'extrémités

(13, 14) complémentaires des plaques de support (15 à 26) et présentant chacune une position vide et des passages pour les courants de fluide.

3. Appareil selon l'une quelconque des revendications 1 et 2, caractérisé en ce qu'il y a quatre passages de dérivation (35 à 38) dans chaque plaque de support (15) et quatre produits de réaction.

4. Appareil selon l'une quelconque des revendications 1 à 3, caractérisé en ce que les plaques de support (15 à 26) sont en polytétrafluoroéthylène.

5. Appareil selon l'une quelconque des revendications précédentes, caractérisé en ce que la chambre de réaction (39) de chaque plaque de support (15 à 26) contient une paire de plaques poreuses espacées (41, 43) entre lesquelles est maintenu le support solide (42).

6. Appareil selon l'une quelconque des revendications précédentes, caractérisé en ce que les plaques de support (15 à 26) sont munies de trous de passage centraux (33) dans lesquels passe une tige pour former un support rotatif des plaques.

7. Appareil selon l'une quelconque des revendications précédentes, caractérisé en ce qu'il comporte également des plaques factices percées d'au moins cinq trous de passage disposés symétriquement, et pas de chambre de réaction.

8. Appareil selon l'une quelconque des revendications précédentes, caractérisé en ce qu'il comprend en outre une tête de rotation de plaque (65, 75) pouvant être utilisée pour s'engager contre une plaque sélectionnée (15 à 26) de manière à faire tourner cette plaque, des moyens (64, 67) pour repérer la tête de rotation (65, 75) pas à pas le long des plaques (15 à 26), et une tige de localisation (63) pourvant s'engager dans l'un d'un ensemble de trous de localisation de chaque plaque, et se repérant pas à pas, de façon que lorsque la tête de rotation vient s'engager contre la $m^{ième}$ plaque dans une pile de n plaques où $1<m<n$, les plaques nouvellement alignées allant de 1 à $(m-1)$ soient engagées par la tige de localisation (63).

9. Appareil selon la revendication 7, caractérisé en ce que la tige de localisation (63) et la tête de rotation de plaque (65) sont entraînées par des vis sans fin entraînées par un moteur d'entraînement et une boîte d'engrenages (67) communs.

10. Appareil selon l'une quelconque des revendications 8 et 9, caractérisé en ce qu'un piston plongeur à double action entraîne la tête de localisation pour l'amener en contact et le retirer du contact avec chaque plaque.

11. Appareil selon l'une quelconque des revendications 8 à 10, caractérisé en ce que les bords des plaques sont munis de marquages optiques et en ce que la tête de rotation de plaque comprend un détecteur détectant le passage des marquages.

12. Appareil selon l'une quelconque des revendications 8 à 10, caractérisé en ce qu'il comprend un piston plongeur (71) pouvant fonctionner pour appliquer une pression aux plaques pendant le passage des produits de réaction, et pour libérer cette pression pendant le repérage.

13. Appareil selon la revendication 12, caractérisé en ce que le piston plongeur (71) comprend un détecteur de position fonctionnant pour détecter une position sortie de ce piston à partir de laquelle on peut détecter le nombre de plaques présentes.

14. Procédé pour effectuer simultanément une multiplicité de synthèses chimiques successives différentes, consistant à utiliser l'appareil selon les revendications 1 à 13, et à régler pour chaque étape les positions des plaques selon les composés à synthétiser, à appliquer la pression aux plaques, à faire passe des courants de produits de réaction à travers les plaques, et à relâcher la pression pour qu'on puisse régler les positions des plaques dans l'étape suivante.

15. Procédé selon la revendication 14, caractérisé en ce que les composés à synthétiser sont des oligonucléotides.

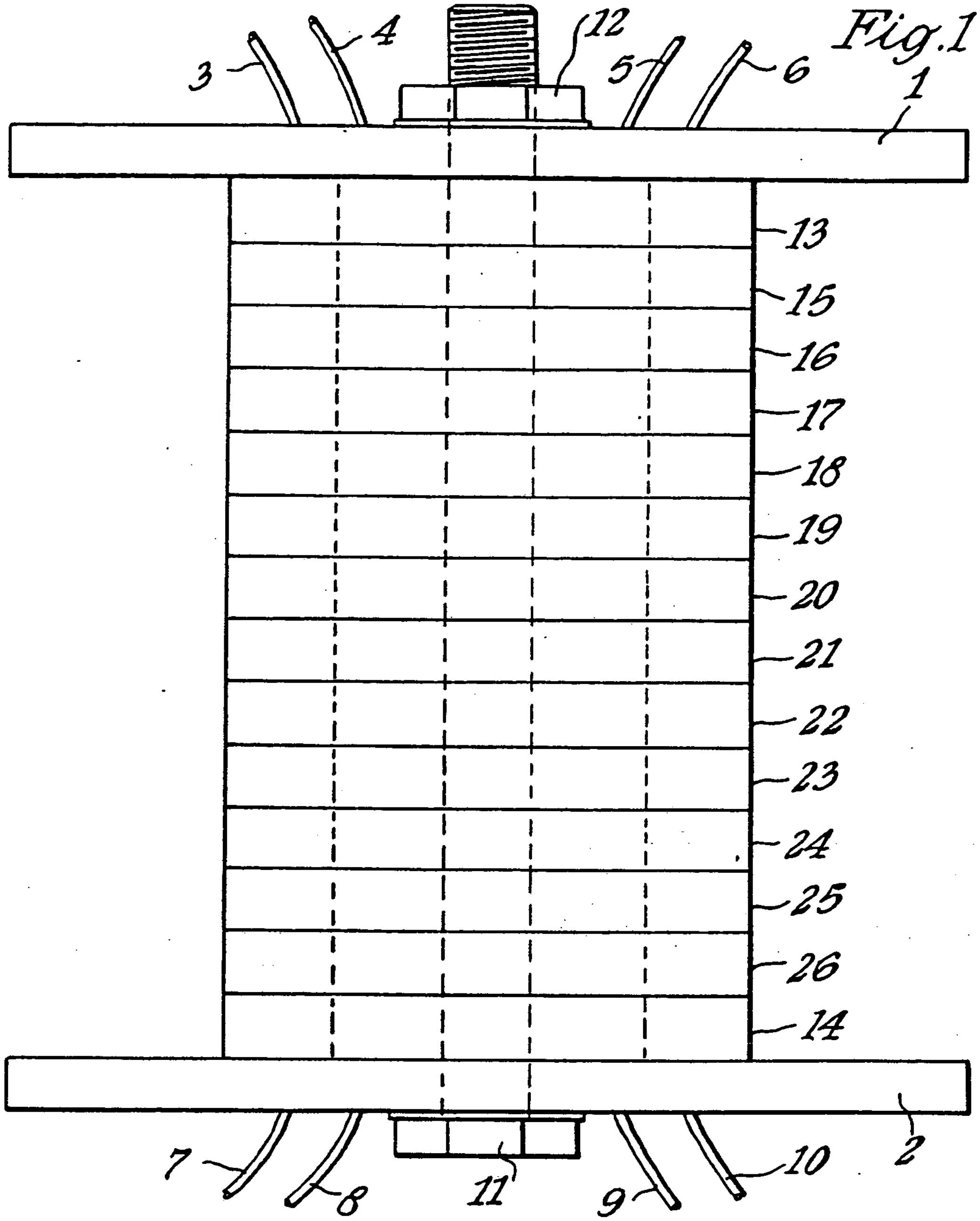

Fig.1

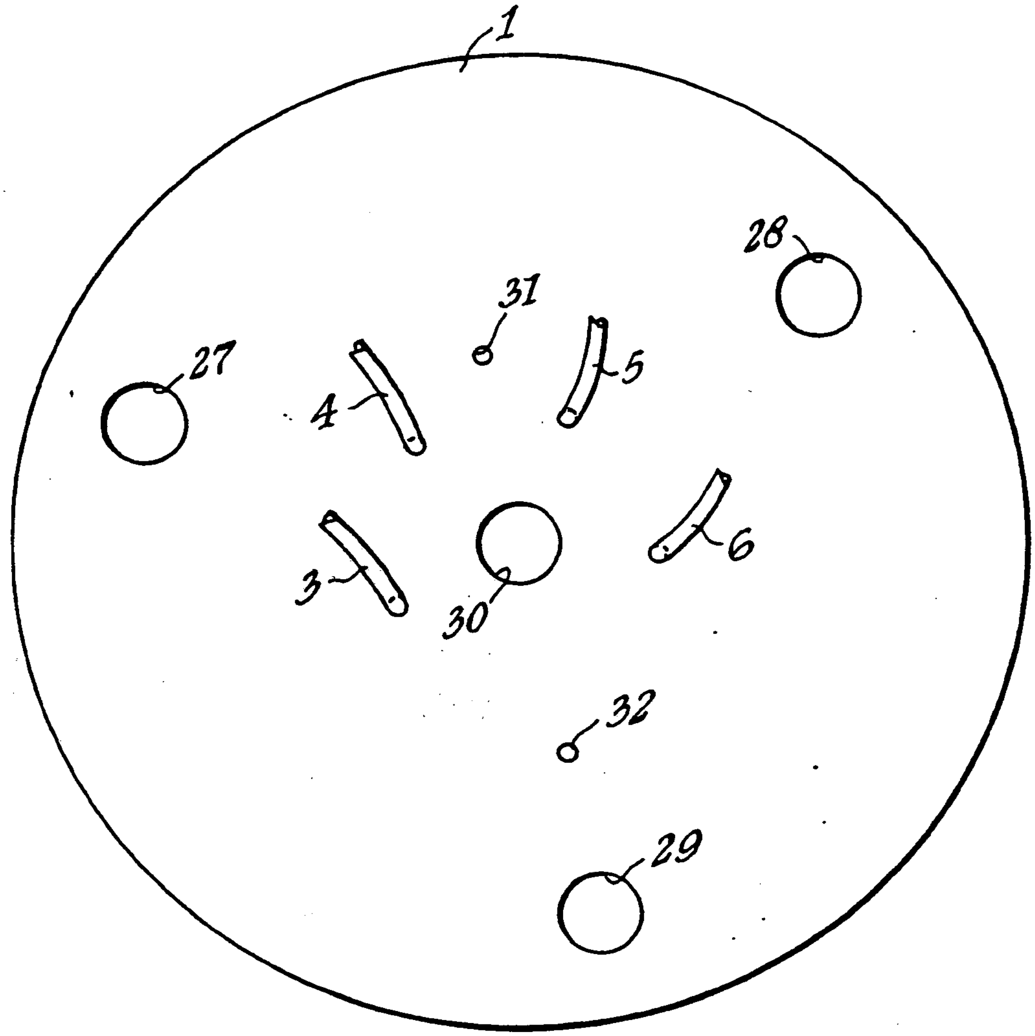

Fig.2.

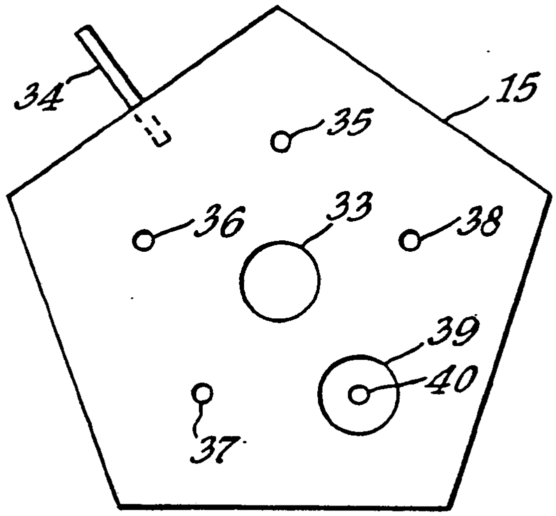

Fig.3.

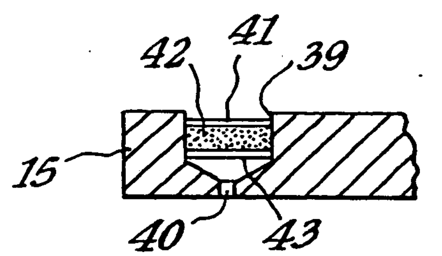

Fig.4.

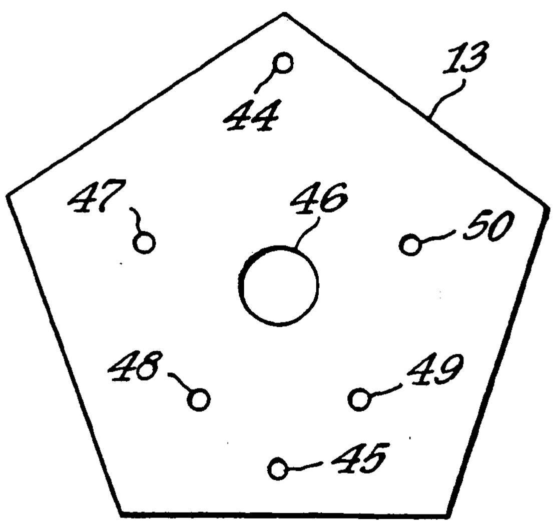

Fig.5.

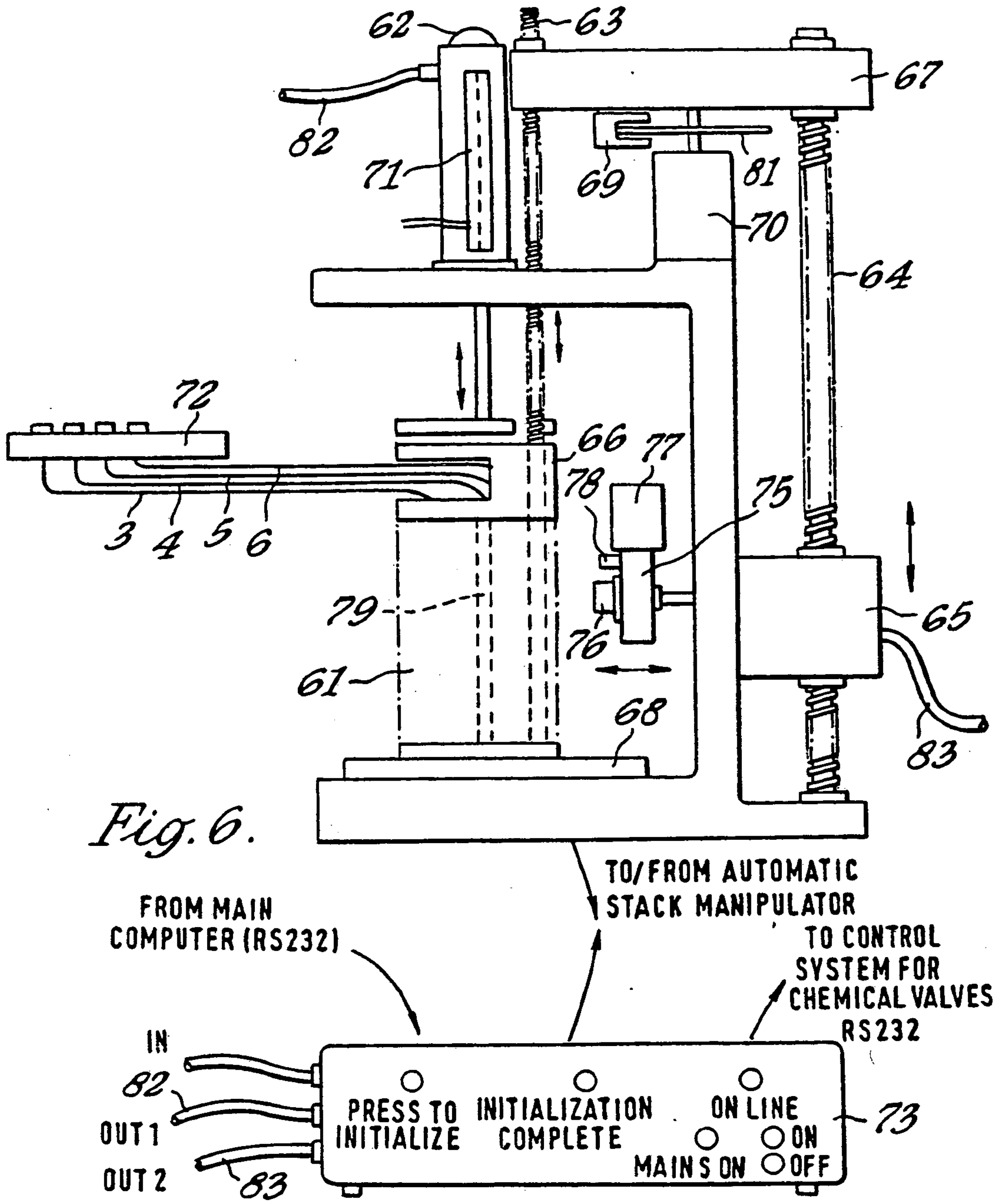
62
63
67
82
71
69
81
70
64
72
66
77
78
75
3
4
5
6
79
65
76
61
68
83
TO/FROM AUTOMATIC STACK MANIPULATOR
FROM MAIN COMPUTER (RS232)
TO CONTROL SYSTEM FOR CHEMICAL VALVES RS232
IN
82
OUT 1
OUT 2
83
PRESS TO INITIALIZE
INITIALIZATION COMPLETE
ON LINE
MAINS ON
ON
OFF
73

Fig. 6.